

This Page Is Inserted by IFW Operations  
and is not a part of the Official Record

## **BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning documents *will not* correct images,  
please do not report the images to the  
Image Problem Mailbox.**



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION  
International Bureau



5704

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : A61K 31/41		A1	(11) International Publication Number: WO 96/40120
			(43) International Publication Date: 19 December 1996 (19.12.96)
(21) International Application Number: PCT/US96/07446		(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).	
(22) International Filing Date: 22 May 1996 (22.05.96)		Published With international search report.	
(30) Priority Data: 08/473,818 7 June 1995 (07.06.95) US			
(71) Applicant: THE PROCTER & GAMBLE COMPANY [US/US]; One Procter & Gamble Plaza, Cincinnati, OH 45202 (US).			
(72) Inventor: CAMDEN, James, Berger, 7339 Charter Cup Lane, West Chester, OH 45069 (US).			
(74) Agents: REED, T., David et al.; The Procter & Gamble Company, 5299 Spring Grove Avenue, Cincinnati, OH 45217 (US).			
(54) Title: USE OF BIS-1,2,4-TRIAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF CANCERS			
(57) Abstract  A pharmaceutical composition that inhibits the growth of tumors and cancers in mammals comprising fungicide is disclosed. The particular fungicide used is a 1,3-bis-triazolyl-2-propanol derivative. These compositions are also effective against viral infections.			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

## USE OF BIS-1,2,4-TRIAZOLES FOR THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF CANCERS

5

## TECHNICAL FIELD

This invention is a pharmaceutical composition that inhibits the growth of cancers and tumors in mammals, particularly in human and warm blooded animals. The composition contains a 1,3-bis-triazolyl-2-propanol derivative.

10

## BACKGROUND OF THE INVENTION

Cancers are the leading cause of death in animals and humans. The exact cause of cancer is not known, but links between certain activities such as smoking or exposure to carcinogens and the incidence of certain types of cancers and tumors has been shown by a number of researchers.

15

Many types of chemotherapeutic agents have been shown to be effective against cancers and tumor cells, but not all types of cancers and tumors respond to these agents. Unfortunately, many of these agents also destroy normal cells. The exact mechanism for the action of these chemotherapeutic agents are not always known.

20

Despite advances in the field of cancer treatment the leading therapies to date are surgery, radiation and chemotherapy. Chemotherapeutic approaches are said to fight cancers that are metastasized or ones that are particularly aggressive. Such cytocidal or cytostatic agents work best on cancers with large growth factors, i.e., ones whose cells are rapidly dividing. To date, hormones, in particular  
25 estrogen, progesterone and testosterone, and some antibiotics produced by a variety of microbes, alkylating agents, and anti-metabolites form the bulk of therapies available to oncologists. Ideally cytotoxic agents that have specificity for cancer and tumor cells while not affecting normal cells would be extremely desirable. Unfortunately, none have been found and instead agents which target especially  
30 rapidly dividing cells (both tumor and normal) have been used.

Clearly, the development of materials that would target tumor cells due to some unique specificity for them would be a breakthrough. Alternatively, materials that were cytotoxic to tumor cells while exerting mild effects on normal cells would be desirable. Therefore, it is an object of this invention to provide a pharmaceutical

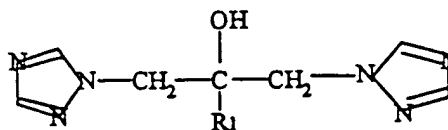
composition that is effective in inhibiting the growth of tumors and cancers in mammals with mild or no effects on normal cells.

More specifically, it is an object of this invention to provide an anti-cancer composition comprising a pharmaceutical carrier and a 1,3-bis-triazolyl-2-propanol derivative as defined herein along with a method for treating such cancers.

These and other objects will become evident from the following detailed description of this inventions.

#### SUMMARY OF THE INVENTION

A pharmaceutical composition for treatment of mammals, and in particular, warm blooded animals and humans, comprising a pharmaceutical carrier and an effective amount anti-cancer compound selected from the group consisting of:



wherein  $R^1$  is an optionally substituted alkyl, cycloalkyl (e.g. cyclopentyl or cyclohexyl), aryl or haloaryl (e.g. phenyl or 2,4-dichlorophenyl) or aralkyl (e.g., benzyl); and salts and metal complexes and ethers or esters thereof, and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. Specifically, such bis triazole derivatives as 2-(2,4-dichlorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)propan-2-ol and its corresponding 2- and 4- chlorophenyl analogs and 2,4-difluorophenyl analogs are claimed.

These compositions can be used to inhibit the growth of cancers, leukemia and other tumors in humans or animals by administration of an effective amount either orally, rectally, topically or parenterally, intravenously or by injection into the tumor. These compositions do not significantly affect healthy cells as compared to adriamycin which has a detrimental effect on healthy cells.

These compositions are also effective against viruses. Therefore it is an object of this invention to provide a composition effective against HIV, herpes, influenza, rhinoviruses and the like.

#### DETAILED DESCRIPTION OF THE INVENTION

**A. Definitions:**

As used herein, the term "comprising" means various components can be conjointly employed in the pharmaceutical composition of this invention. Accordingly, the terms "consisting essentially of" and "consisting of" are embodied  
5 in the term comprising.

As used herein, a "pharmaceutically acceptable" component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

10 As used herein, the term "safe and effective amount" refers to the quantity of a component which is sufficient to yield a desired therapeutic response without undue adverse side effects (such as toxicity, irritation, or allergic response) commensurate with a reasonable benefit/risk ratio when used in the manner of this invention. The specific "safe and effective amount" will, obviously, vary with such  
15 factors as the particular condition being treated, the physical condition of the patient, the type of mammal being treated, the duration of the treatment, the nature of concurrent therapy (if any), and the specific formulations employed and the structure of the compounds or its derivatives.

As used herein, a "pharmaceutical addition salts" is salt of the anti-cancer  
20 compound with an organic or inorganic acid. These preferred acid addition salts are chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates, and the like.

As used herein, a "pharmaceutical carrier" is a pharmaceutically acceptable solvent, suspending agent or vehicle for delivering the anti-cancer agent to the  
25 animal or human. The carrier may be liquid or solid and is selected with the planned manner of administration in mind.

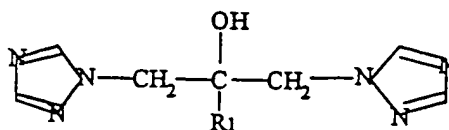
As used herein, "cancer" refers to all types of cancers or neoplasm or malignant tumors, including leukemia, found in mammals.

As used herein, the "anti-cancer compounds" are the 1,3-bis-triazolyl-2-  
30 propanols, and their salts. The exact 1,3-bis-triazolyl-2-propanols are described in detail below. The preferred materials are the products sold under the names "fluconazole®" by Pfizer.

As used herein, "viruses" includes viruses which cause diseases (viral infection) in man and other warm blooded animals such as HIV virus, herpes,  
35 influenza and rhinoviruses.

## B. THE ANTI-CANCER COMPOUNDS

The anti-cancer compounds are 1,3-bis-triazolyl-2-propanol derivatives which are known for their antifungal activities. They are systemic fungicides used to prevent and eradicate fungi. The compounds have the following structure:



wherein R<sup>1</sup> is an optionally substituted alkyl, cycloalkyl (e.g. cyclopentyl or cyclohexyl), aryl or haloaryl (e.g. phenyl or 2,4-dichlorophenyl) or aralkyl (e.g., benzyl); and salts and metal complexes and ethers or esters thereof, and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids. Specifically, such bis triazole derivatives as 2-(2,4-dichlorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)propan-2-ol and its corresponding 2- and 4-chlorophenyl analogs and 2,4-difluorophenyl analogs are useful herein. Preferably the composition is 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol and its pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

These compounds are prepared according to the method described in U.S. 4,404,216 issued to Richardson, Sept. 13, 1983 and British Patent Application No. 2,078,719A published Jan. 13, 1982 and European patent application No. 44,605 published Jan. 27, 1982 (both assigned to Imperial Chemical Industries Ltd).

It is believed that these particular fungicides have the capability of reducing tumors or decreasing their growth significantly because of their ability to inhibit the synthesis of sterols.

## C. DOSAGE

Any suitable dosage may be given in the method of the invention. The type of compound and the carrier and the amount will vary widely depending on the species of the warm blooded animal or human, body weight, and tumor, virus, cancer or disease being treated. Generally a dosage of between about 2 milligrams (mg) per kilogram (kg) of body weight and about 400 mg per kg of body weight is suitable. Preferably from 15 mg to about 150 mg/kg of body weight is used. Generally, the dosage in man is lower than for small warm blooded mammals such as mice. A dosage unit may comprise a single compound or mixtures thereof with other compounds or other cancer inhibiting compounds. The dosage unit can also comprise diluents, extenders, carriers and the like. The unit may be in solid or gel form such as pills, tablets, capsules and the like or in liquid form suitable for oral,



rectal, topical, intravenous injection or parenteral administration or injection into or around the tumor.

#### D. DOSAGE DELIVERY FORMS

The anti-cancer compounds are typically mixed with a pharmaceutically acceptable carrier. This carrier can be a solid or liquid and the type is generally chosen based on the type of administration being used. The active agent can be coadministered in the form of a tablet or capsule, as an agglomerated powder or in a liquid form. Examples of suitable solid carriers include lactose, sucrose, gelatin and agar. Capsule or tablets can be easily formulated and can be made easy to swallow or chew; other solid forms include granules, and bulk powders. Tablets may contain suitable binders, lubricants, diluents, disintegrating agents, coloring agents, flavoring agents, flow-inducing agents, and melting agents. Examples of suitable liquid dosage forms include solutions or suspensions in water, pharmaceutically acceptable fats and oils, alcohols or other organic solvents, including esters, emulsions, syrups or elixirs, suspensions, solutions and/or suspensions reconstituted from non-effervescent granules and effervescent preparations reconstituted from effervescent granules. Such liquid dosage forms may contain, for example, suitable solvents, preservatives, emulsifying agents, suspending agents, diluents, sweeteners, thickeners, and melting agents. Oral dosage forms optionally contain flavorants and coloring agents. Parenteral and intravenous forms would also include minerals and other materials to make them compatible with the type of injection or delivery system chosen.

Specific examples of pharmaceutical acceptable carriers and excipients that may be used to formulate oral dosage forms of the present invention are described in US. Pat. No. 3,903,297 to Robert, issued Sept. 2, 1975. Techniques and compositions for making dosage forms useful in the present invention are described in the following references: 7 Modern Pharmaceutics, Chapters 9 and 10 (Banker & Rhodes, Editors, 1979); Lieberman et al., Pharmaceutical Dosage Forms: Tablets (1981); and Ansel, Introduction to Pharmaceutical Dosage Forms 2nd Edition (1976).

#### E. METHOD OF TREATMENT

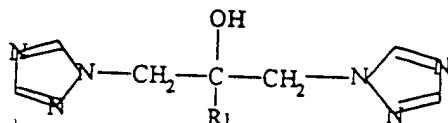
The method of treatment can be any suitable method which is effective in the treatment of the particular cancer or tumor type or virus that is being treated. Treatment may be oral, rectal, topical, parenteral or intravenous administration or by injection into the tumor and the like. The method of applying an effective amount also varies depending on the tumor being treated. It is believed that

parenteral treatment by intravenous, subcutaneous, or intramuscular application of the 1,3-bis-triazolyl-2-propanol compounds, formulated with an appropriate carrier, additional cancer inhibiting compound or compounds or diluent to facilitate application will be the preferred method of administering the compounds to warm  
5 blooded animals.

5704

WHAT IS CLAIMED IS:

1. A pharmaceutical composition for treating cancers, tumors, viruses comprising a safe and effective amount of:



wherein R<sup>1</sup> is an optionally substituted alkyl, cycloalkyl (e.g. cyclopentyl or cyclohexyl), aryl or haloaryl (e.g. phenyl or 2,4-dichlorophenyl) or aralkyl (e.g., benzyl); and salts and metal complexes and ethers or esters thereof, and the non-toxic, pharmaceutically acceptable acid addition salts with both organic and inorganic acids.

2. A pharmaceutical composition according to Claim 1 comprising a pharmaceutically acceptable carrier and a safe and effective amount of a 1,3-bis-triazolyl-2-propanol selected from the group consisting of: 2-(2,4-dichlorophenyl)-1,3-bis(1H-1,2,4-triazole-1-yl)propan-2-ol and its corresponding 2- and 4- chlorophenyl analogs and 2,4-difluorophenyl analogs, and 2-(2,4-difluorophenyl)-1,3-bis(1H-1,2,4-triazol-1-yl)propan-2-ol and the pharmaceutically acceptable acid addition salts with both organic and inorganic acids.
3. A pharmaceutical composition according to Claim 1 or 2 for inhibiting the growth of tumors and for treating leukemia.
4. A pharmaceutical composition according to Claim 1, 2 or 3 wherein said pharmaceutical acceptable acid addition salts are selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and mixtures thereof.

5. A method of treating cancer and viral infections in warm blooded mammals comprising administering 2 mg/kg body weight to 400 mg/kg of a 1,3-bis-triazolyl-2-propanol according to Claim 1, 2 or 4
6. A method according to Claim 5 wherein said 1,3-bis-triazolyl-2-propanol is administered orally or enterically, intravenously, parenterally, parenterally or by injection into the tumor.
7. A method according to Claim 6 wherein said 1,3-bis-triazolyl-2-propanol is administered in a solid form wherein said solid form includes a carrier selected from the group consisting of lactose, sucrose, gelatin and agar.
8. A method according to Claim 6 wherein said 1,3-bis-triazolyl-2-propanol is administered in a liquid form, wherein said liquid dosage form is selected from the group consisting of aqueous solutions, alcohol solutions, emulsions, suspensions, and suspensions reconstituted from non-effervescent and effervescent preparations and suspensions in pharmaceutically acceptable fats or oils.
9. A method according to Claim 6, 7 or 8 wherein said pharmaceutically acceptable acid addition salts are selected from the group consisting of chlorides, bromides, sulfates, nitrates, phosphates, sulfonates, formates, tartrates, maleates, malates, citrates, benzoates, salicylates, ascorbates and mixtures thereof.
10. A unit dosage composition for treating viral infections and cancer in animals or humans comprising a 1,3-bis-triazolyl-2-propanol according to Claims 1 or 2.

# INTERNATIONAL SEARCH REPORT

International Application No.

PCT/US 96/07446

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 A61K31/41

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BE 1 004 029 A (DE MOL, OMER) 8 September 1992 see claims 1,4,22 ---	1-10
P,X	BIOCHEM. PHARMACOL., vol. 50, no. 7, 28 September 1995, pages 923-928, XP002009214 EDWARD L. SCHWARTZ ET AL.: "Inhibition of all-trans retinoic acid metabolism by fluconazole in vitro and in patients with acute promyelocytic leukemia" see abstract ---	1-10
X	EP 0 044 605 A (IMPERIAL CHEMICAL INDUSTRIES LIMITED) 27 January 1982 cited in the application see page 1, line 10 - line 12 see page 19, paragraph 2-4; claims 1-7 ---	1-4,10
-/-		

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

### \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

- \*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- \*Z\* document member of the same patent family

Date of the actual completion of the international search

24 July 1996

Date of mailing of the international search report

02.09.96

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 631 epo nl,  
Fax: (+31-70) 340-3016

Authorized officer

Tzschoppe, D

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/US 96/07446

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 4 404 216 A (KENNETH RICHARDSON) 13 September 1983 cited in the application see column 4, paragraph 2-4; claims 1-3 -----	1-4,10